82259.1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Rahal, James

Examiner: Winkler, Ulrike

Serial No.: 09/935,966

Group Art Unit: 1648

Filed: August 23, 2001

Docket No.: 13099

For: Methods of Preventing or Treating West Nile Virus and Other Infections

Customer No.: 23719

Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, NY 10022

February 2, 2005

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

DECLARATION OF DR. JAMES J. RAHAL

I, Dr. James J. Rahal, hereby declare that:

1. I am the inventor of the above-identified application.

2. I received my A.B in Biology from Harvard College in 1955 and my M.D. degree from Tufts University School of Medicine in 1959. I have worked extensively since at least as early as 1963 in the Infectious Diseases field. I have authored numerous publications including textbook chapters in the Infectious Diseases field. Since 1988, I have been Director of the Infectious Disease Section at The New York Hospital Medical Center of Queens. I am also Professor of Medicine and Assistant Dean at Weill College of Medicine, Cornell University. A copy of my curriculum vitae is attached.

3. I submit this declaration based upon: (i) my training, knowledge, education, and experience in the Infectious Diseases field; (ii) my review of the above-referenced application and the history of the prosecution of this application; and (iii) the clinical trial conducted which shows that interferon alpha-2b treatment for West Nile Virus meningo-encephalitis, an infection causing the combination of meningitis and encephalitis, resulted in significantly improved neurological functional status, a sign that the infection is resolving.

5. I disagree with the Examiner's opinion that there is lack of enablement for the administration of interferon alpha-2b via the parenteral route for the treatment of West Nile Viral (WNV) meningitis, encephalitis, or meningo-encephalitis discussed in the June 4, 2004 Final Office Action at page 6.

6. In order to assess whether interferon alpha-2b was effective for the treatment of WNV meningo-encephalitis, a randomized, unblinded, multi-institutional clinical study was conducted using the protocol I developed and that is described in Example 3 of the specification at pages 14-16. The dose and route of administration of interferon alpha-2b was 3 million units intravenously (IV) initially; then 3 million units subcutaneously 12 hours later, then 3 million units subcutaneously every 24 hours for up to 14 days of therapy (as described on page 15, lines 14-20 of the specification).

7. The clinical study methods were as follows:

a) Patient Enrollment:

During the summers of 2002-2003, patients with clinical and epidemiologic evidence of WNV meningo-encephalitis were enrolled. Patients were randomly assigned into two groups: group 1 received interferon alpha-2b for two weeks (6 million units initially-3 million units intravenously (IV) initially; then 3 million units subcutaneously12 hours later) followed by 3 million units daily plus standard supportive therapy; group 2 did not receive interferon, but received standard supportive therapy alone. Treatment was initiated prior to the results of WNV serologic studies. Patients with serologically-proven WNV infection and follow-up examination after 3 weeks were included in the outcome analysis.

b) Interferon Dose Regimen

IV interferon alpha-2b was given at a dose of 3 million units initially; then 3 million units by subcutaneous injection 12 hours later, followed by 3 million units subcutaneously every 24 hours to complete up to 14 days of therapy if tolerated. The interferon alpha-2b in the clinical study was given by the intravenous and subcutaneous route and **not** by intracranial administration.

c) Clinical Evaluation of Outcome:

19 patients were randomized to each group. Among the interferon treated patients, 2 were seronegative, 1 was lost to follow up, and 1 died within the first 36 hours. Among the patients that did not receive interferon, 4 patients were seronegative, 4 were lost to follow up, and three withdrew. Thus, 15 interferon treated and 8 patients that did not receive interferon were eligible for analysis. The evaluation of outcome was determined by assessment of neurologic status at enrollment, using the National Institute of Health Stroke Scale (N.I.H.S.S.), which provides an initial functional score of 0 or negative number (lowest function) to 42 (highest function). The neurologic examination is scored with the N.I.H.S.S. to quantify the degree of neurologic dysfunction from the WNV infection. Neurologic dysfunction is the result of active viral invasion of the CNS causing inflammation and ultimate cell destruction. Resolution of neurologic dysfunction is a sign of resolving infection. A high N.I.H.S.S. score correlates with a large neurologic dysfunction. In the clinical study, this scale was used to assess whether CNS infection, such as a meningitis or encephalitis, is resolving. Subsequent examinations help quantify the progress of the patient. Typically, the patient is assessed and scored as follows:

Level of Consciousness
0 = Alert, keenly responsive
1= Drowsy, arousable by minor stimulation to obey, answer, or respond
2 = Responds only with reflex motor or autonomic effects, or totally unresponsive

Level of Consciousness Question: Patients are asked the month and their age
0 = Both correct or language barrier
1= One correct
2 = Both incorrect, or unable to respond

Level of Consciousness Command: The patient is asked to close the eye and the hand
0 = Both correct or language barrier
1= One correct
2 = Both incorrect, or unable to respond

Best Visual: Test vision in each field to finger movement simultaneously
0 = Normal or old blindness
1= Asymmetry or partial hemianopia
2 = Complete hemianopia
3 = Bilateral hemianopia or coma

Best Gaze
0 = Full range of eye movements
1= Partial gaze palsy or isolated nerve palsy
2 = Forced deviation or total gaze paresis not overcome by Doll's eye maneuver

Facial weakness
0 = None or sedated
1 = minor (just loss of naso-labial fold)
2 = Partial (lower half of the face)
3 = Complete (all half involved) or coma

Best Motor Left Arm: The patient holds the arm outstretched at 90 degrees.
0 = Limb holds 90 degrees for full 10 seconds, effusion or amputation
1= Limb holds 90-degree position, but drifts before full 10 seconds
2 = Limb cannot hold 90-degree position for full 10 seconds, some effort against gravity
3 = Limb falls, no effort against gravity
4 = No movement

Best Motor Right Arm: The patient holds the arm outstretched at 90 degrees.
0 = Limb holds 90 degrees for full 10 seconds, effusion or amputation
1= Limb holds 90-degree position, but drifts before full 10 seconds
2 = Limb cannot hold 90-degree position for full 10 seconds, some effort against gravity
3 = Limb falls, no effort against gravity
4 = No movement

Best Motor Left Leg: The patient elevates the leg at 30 degrees for 5 seconds.
0 = Leg holds 30-degree position for 5 seconds, effusion or amputation
1= Leg falls to intermediate position by end of 5 seconds
2 = Leg falls to bed by 5 seconds, some effort against gravity
3 = Leg falls to bed immediately, no resistance against gravity
4 = No movement

Best Motor Right Leg: The patient elevates the leg at 30 degrees for 5 seconds.
0 = Leg holds 30-degree position for 5 seconds, effusion or amputation
1= Leg falls to intermediate position by end of 5 seconds
2 = Leg falls to bed by 5 seconds, some effort against gravity

3 = Leg falls to bed immediately, no resistance against gravity
4 = No movement

Limb Ataxia: Finger-to-nose and heel-to-shin test
0 = Absent (no movement of limb), can not be examined
1= Ataxia present in one limb
2 = Ataxia present in two limbs
Sensory: Pin prick. If level of consciousness is impaired, score only if a grimace or asymmetric withdrawal is present.
0 = Normal, sedated or amputation
1= Mild to moderate. Patient feels pin prick less sharp, but is aware of being touched
2 = Severe to total sensation loss, not aware of being touched

Neglect
0 = No neglect or sedated
1= Visual, tactile, or auditory hemi-inattention
2 = Profound hemi-inattention to more than one modality

Dysarthria
0 = Normal
1= Mild to moderate slurring of words, can be understood
2 = Speech slurred, unintelligible

Best Language: Standard pictures are named.
0 = Normal
1= Mild to moderate naming errors, word-finding errors, or paraphasias. Impairment of communication by either comprehension or expression.
2= Severe: fully developed Broca's (expressive) or Wernicke's (receptive) aphasia
3 = Mute or global aphasia or coma.

The N.I.H.S.S. in this trial was determined again at 1, 2, and 3 weeks after enrollment. The difference between the functional score at enrollment and after 3 weeks was determined for each group. The effectiveness of interferon alpha-2b was determined by a comparison of the mean change in N.I.H.S.S. scores among interferon treated patients and patients that did not receive interferon.

d) **Results:**

The change in N.I.H.S.S. for the interferon treated patients at 3 weeks after enrollment is shown in Table 1 and untreated patients is shown in Table 2.

Table 1
Neurological Score After 3 Weeks For Patients Given Interferon

Patient No.	Neurological Score (0 to +23)	Interferon Dose And Length Of Treatment	Age (M/F)	Serum +/-
1	+5	14	74 M	+
2	0	14	53 M	+
3	+6	10	81 F	+
4	+7	12	81 M	+
5	+5	14	40 M	+
6	+20	14	73 F	+
7	+20	14	75 M	+
8	+6	10	83 F	+
9	+2	14	45 M	+
10	+8	10	76 F	+
11	+12	14	47 M	+
12	+23	14	85 F	+
13	+7	14	66 M	+
14	+12	14	25 M	+
15	+11	14	73 M	+
Mean	+9.6 (p=.008)	13.1	Age 65.1	All positive

Table 2
Neurological Score After 3 Weeks For Patients Not Given Interferon

Patient No.	Score (-1 to +8)	Age (M/F)	Serum +/-
1	+6	74 M	+
2	+2	65 F	+
3	+3	68 M	+
4	+1	57 F	+
5	+1	71 M	+
6	+4	80 M	+
7	-1	62 M	+
8	+8	62 M	+
Mean	+3.0 (p=.008)	Age 67.4	All positive

Changes designated with a plus sign indicate the degree of improvement, and by a minus sign indicate the degree of deterioration, on a scale of 0-42. The mean improvement among 15 treated patients was +9.6 and among 8 untreated patients, +3.0. This difference is statistically significant ($p = 0.008$ by 2-tailed Fisher's randomization test) with a confidence of greater than 95%. Alpha-2b interferon was given for an average of 13.1 days. The most common adverse events were elevation of serum transaminase and neutropenia. Grade 3 hepatotoxicity occurred in 37.5% of the patients, and grade 3 neutropenia in 31% of the patients. These events resolved with drug cessation.

e) **Conclusion:**

Treatment of patients with West Nile viral meningitis or encephalitis with interferon alpha-2b by the IV route for up to 14 days results in a significantly improved neurologic functional status and survival after three weeks, as compared to patients that did not receive the interferon alpha-2b.

8. Thus, following my protocol described in Example 3 of the specification, for example page 15, lines 14-20, one of ordinary skill in the art can use interferon alpha-2b IV, initially, followed by subcutaneous injections for the successful treatment of WNV meningo-encephalitis. Again, the interferon alpha-2b is not administered by the intracranial route, but by the IV route at a dose of 3 million units IV initially; then 3 million units subcutaneously 12 hours later, then followed by 3 million units subcutaneously every 24 hours for up to 14 days of therapy. Accordingly, the specification clearly enables this treatment and the clinical trial further supports this treatment protocol.

9. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. All statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

James Rahal

Dr. James J. Rahal

2/2/05

Date

CURRICULUM VITAE

NAME: James J. Rahal, Jr.

BORN: Boston, Massachusetts; October 14, 1933

EDUCATION: Harvard College, A.B. cum laude, 1955

Tufts University School of Medicine, M.D. cum laude. Alpha Omega Alpha, 1959

POSTGRADUATE TRAINING:

Intern and Assistant Resident in Medicine
Second (Cornell) Medical Division
Bellevue Hospital, New York, N.Y. - 1959-1961.

Senior Resident in Medicine
New England Medical Center Hospitals - 1961-1962.

Chief Resident In Infectious Diseases
New England Medical Center Hospitals - 1963-1964

U.S.P.H.S Trainee in Infectious Diseases - New England Medical Center Hospitals - 1962-1963; 1964-1965.

FULL TIME APPOINTMENTS:

Assistant Physician, Department of Medicine and Infectious Disease Service, New England Medical Center Hospitals 1965-1969.

Instructor in Medicine, Tufts University School of Medicine 1965-1966.

Senior Instructor in Medicine, Tufts University School of Medicine - 1966-1968.

Assistant Professor of Medicine, Tufts University School of Medicine - 1968-1969

Assistant Professor of Medicine, New York University School of Medicine - 1969-1974.

Chief, Division of Infectious Disease, Manhattan Veterans Administration Medical Center - 1969-1986.

Chief, Infectious Disease Section, New York Infirmary Beekman Downtown Hospital 1986-1988.

Associate Professor of Medicine, New York University School of Medicine - 1974-1989.

Director, Infectious Disease Section, The New York Hospital Medical Center of Queens, formerly Booth Memorial Medical Center - 1988-present.

Associate Professor of Medicine, Albert Einstein College of Medicine - 1988-1991.

Visiting Professor of Medicine, Albert Einstein College of Medicine - 1994-present.

Professor of Medicine, Albert Einstein College of Medicine - 1991-1992.

Clinical Professor of Medicine, Weill College of Medicine, Cornell University - 1992-2000.

Professor of Medicine, Weill College of Medicine, Cornell University - 2001-present.

Assistant Dean, Weill College of Medicine, Cornell University - 2004-Present

Director, Certified Infectious Disease Training Programs:

New York (Manhattan) V.A. Medical Center 1970-1986
New York Hospital Medical Center of Queens 1988-present

SPECIALTY BOARDS:

American Board of Internal Medicine - 1967
American Board of Infectious Diseases - 1972

RESEARCH AWARDS:

Research Fellowship - Medical Foundation of Boston - 1966-1968
Principal Investigator - USPHS Research Grant #AI-07066 "Mechanism of Action of Bacterial Exotoxins" 1966-1969

Principal Investigator - Veterans Administration Research Grant - "Biochemical Mechanisms in Septic Shock: The Role of Bacterial Toxins" 1971-1978

Chairman - V.A. Cooperative Study #89 - "Nafcillin Therapy of Staphylococcal Bacteremia: Four week versus six week therapy for staphylococcal endocarditis and two week versus four week therapy for bacteremia without evidence of endocarditis" - 1978-1981

Albion O. Bernstein, MD Award - April 17, 2004 - Presented by the Medical Society of the State of New York in recognition of identification, treatment and prevention of nosocomial infection with multi-drug resistant gram negative organisms.

TEACHING AWARDS:

Teacher of the year Award-Booth Memorial Medical Center Medical Housestaff - 1988-1989

First Annual Infectious Disease Fellows Award-Albert Einstein College of Medicine - 1991-1992

RESEARCH APPOINTMENT:

Visiting Investigator, Department of Biochemistry, Public Health Research Institute of the City of New York, 1969-1970

SCIENTIFIC SOCIETIES:

Fellow-Infectious Diseases Society of America

President, New York Society of Infectious Diseases 1996-97.

Fellow-American College of Physicians

American Federation for Clinical Research

American Society for Microbiology

American Association for the Advancement of Science

PROFESSIONAL COMMITTEES - REGIONAL AND NATIONAL:

Advisory Expert Committee on Infectious Disease Control - New York City Department of Health, Member, 1974-1985

Veterans Administration Advisory Committee on Infectious Disease, V.A. Central Office, Washington, D.C., Member, 1976-1981

New York State AIDS Institute - Subcommittee on Access to Therapeutic Trials - Member, 1987-1988

New York State Chapter, American College of Physicians - AIDS Subcommittee of the Health and Public Policy Committee - Member, 1988.

National Institute of Health - Data and Safety Monitoring Board for AIDS Treatment Evaluation Units - Member, 1988-1996

New York State Department of Health AIDS Institute: AIDS Drug Assistance Program - Chairman, Medical Advisory Council 1991-1993.

New York State Department of Health AIDS Institute: HIV Uninsured Care Programs-Member, Steering Committee and Chairman, Clinical Subcommittee - 1993-2001.

EDITORIAL BOARD MEMBER

Microbial Drug Resistance
Current Treatment Options in Infectious Diseases
Infectious Disease News

EDITORIAL REVIEWER

New England Journal of Medicine
Journal American Medical Association
Annals of Internal Medicine
Archives of Internal Medicine
Journal of Infectious Diseases
Clinical Infectious Diseases
The Medical Letter

INVITED LECTURES - NATIONAL OR INTERNATIONAL MEETINGS:

Rahal, J. - Treatment of Fungal Endocarditis Conference on Treatment of Bacterial Endocarditis. American Heart Association National Center, Dallas, Texas - April 28-30, 1980.

Rahal, J. - Staphylococcal Bacteremia and Endocarditis. Symposium on Current Problems in Staphylococcal Infections. 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans Louisiana - September 22-24, 1980.

Rahal, J.- Meningitis in Adults. Symposium on Bacterial Meningitis 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois - November, 1981.

Rahal, J. - Teaching Staff. International Course on the Evaluation of Antibiotic Resistance Mechanisms: The Methicillin Resistant *Staphylococcus aureus*. Gulbenkian Institute of Science and Rockefeller University, Oeiras, Portugal, July 22, - August 2, 1991.

Rahal, J. - Antimicrobial resistance in Gram-Negative Pathogens: a Global View: Table Ronde Roussel UCLAF, No. 75, Microbial Antibiotic Resistance: Challenge to Science and Chemotherapy. Versailles, France. July 5-6, 1993.

Rahal, J. - Teaching Staff. Salzburg Cornell Seminar in Infectious Diseases. Soros Foundation, Salzburg, Austria. July 13-20, 1996.

Rahal J. - *Acinetobacter*: Fertile soil for the Emergence of Antibiotic Resistance. Infectious Diseases Society of America, Denver, Colorado. November 12, 1998.

Rahal J. Squeezing the antibiotic resistance balloon: Is it inevitable? 41st Interscience Conference Conference Antimicrobial Agents and Chemotherapy, Chicago, Illinois -September, 2001.

Rahal J. Prevention of antibiotic resistance in hospitals. Meet the Experts Session. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois - September, 2001.

Rahal J. Effects of Interferon Alpha-2b on St. Louis Virus Meningoencephalitis. National Institute of Allergy and Infectious Diseases Symposium on West Nile infection. Bethesda, Md. 11/21/02.

Rahal, J. Emerging Resistance in Nosocomial Pathogens - Multidrug-resistant *Acinetobacter* and *Pseudomonas*. International Conference on Emerging Infectious Diseases. Centers for Disease Control and Prevention, Atlanta, GA. 3/1/04.

Rahal J. Combination Therapy for Multiply Resistant *Acinetobacter* and *Pseudomonas*. Update on Serious Gram Negative Bacterial Infections in the I.C.U. University of Pittsburgh, Pittsburgh, PA. 5/8/04

Rahal, J. Epidemiology and Control of Carbapenem Resistance. Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology. Washington, D.C. 10/31/04

BIBLIOGRAPHY

1. Rahal JJ Jr, Plaut ME, Rosen H, Weinstein L. Purified Staphylococcal Alpha Toxin: Effect on Epithelial Ion Transport. Science 155:1118, 1967.

2. Rahal JJ Jr, Plaut ME, Weinstein L. Effect of Purified Staphylococcal Alpha Toxin on Active Sodium Transport and Aerobic Respiration in the Isolated Toad Bladder. J Clin Invest 47:1603, 1968.

3. Rahal JJ Jr, MacMahon HE, Weinstein L. Thrombocytopenia and Symmetrical Peripheral Gangrene in Staphylococcal and Streptococcal Bacteremia. Ann Int Med 69:35, 1968.

4. Rahal JJ Jr, Meyers B, Weinstein L. Treatment of Bacterial Endocarditis with Cephalothin. N Eng J Med 279:1305, 1968.

5. Rahal JJ Jr, Keusch GT, Weinstein L. Uncoupling of Oxidative Phosphorylation by Purified Staphylococcal Alpha Toxin. J Lab Clin Med 75:442, 1970.

6. Keusch G Rahal JJ Jr, Weinstein L, Grady GF. Biochemical Effects of Cholera Enterotoxin: Oxidative Metabolism in the Infant Rabbit. Am J Physiol 218:703, 1970.

7. Rahal JJ Jr, Henle G. Infectious Mononucleosis and Reye's Syndrome: A Fatal Case with Studies for Epstein-Barr Virus. Pediatrics 46:776, 1970.

8. Rahal JJ Jr, Meade RH III, Bump C, Reinauer A. Upper Respiratory Carriage of Gram-Negative Enteric Bacilli by Hospital Personnel. JAMA 214:754, 1970.

9. Smithivas T, Hyams PJ, Rahal JJ Jr. Gentamicin and Ampicillin in Human Bile. J Infect Dis 124:S106, 1971.

10. Smithivas T, Hyams PJ, Matalon R, Simberkoff MS,Rahal JJ Jr. The Use of Gentamicin in Peritoneal Dialysis. I. Pharmacologic Results. J Infect Dis 124:S77, 1971.

11. Hyams PJ, Smithivas T, Matalon R, Katz L, Simberkoff MS, Rahal JJ Jr. The Use of Gentamicin in Peritoneal Dialysis. II Microbiologic and Clinical Results. J Infect Dis 124:S84, 1971.

12. Rahal JJ Jr. Rat Bite Fever. Current Therapy 1972.

13. Rahal JJ Jr. Comparative Effects of Purified Staphylococcal Alpha and Delta Toxin on Mitochondrial Metabolism. J Inf Dis 126:96, 1972.

14. Rahal JJ Jr. Treatment of Gram Negative Bacillary Meningitis in Adults. Ann Intern Med 77:295, 1972.

15. Hyams PJ, Simberkoff MS, Rahal JJ Jr. *In vitro* Bactericidal Effectiveness of Four Aminoglycoside Antibiotics. Antimicrob Agents and Chemotherapy 3:87-94, 1973.

16. Rahal JJ Jr. *In vitro* Effects of Staphylococcal Alpha and Delta Toxins on Liver Mitochondria. Staphylococcal Infections. Recent Progress. Edit. by Jeljaszewicz. Polish Medical Publishers 1973 pp.345-51.

17. Simberkoff M S, Rahal J J Jr. Acute and Subacute Endocarditis Due to *Erysipelothrix rhusiopathiae*. Amer J Med Sci 266: 53-57, 1973.

18. Rahal JJ Jr, Simberkoff MS, Hyams PJ. *Pseudomonas cepacia* Tricuspid Endocarditis; Treatment with Trimethoprim, Sulfonamide and Polymyxin B. J Infect Dis 128:S762-S767, 1973.

19. Simberkoff MS, Isom OW, Smithivas T, Noriega ER,Rahal JJ Jr. Two-Stage Tricuspid Valve Replacement for Mixed Bacterial Endocarditis. Arch Int Med 133:212-16, 1974.

20. Rahal JJ Jr, Hyams PJ, Simberkoff MS, Rubinstein E. Combined Intrathecal and Intramuscular Gentamicin for Gram Negative Meningitis: Pharmacologic Study of Twenty-One Patients. New Eng J Med 290:1394-98, 1974.

21. Rahal JJ Jr. Bacteremia (Septicemia). Current Therapy. Edit by H.F. Conn. W.B. Saunders, Co. 1974. pp.5-10.

22. Noriega ER, Simberkoff MS, Gilroy FJ, Rahal JJ Jr. Life-threatening *Mycoplasma Pneumonia*. JAMA 229:1471-72, 1974.

23. Rubinstein E, Noriega ER, Simberkoff MS, Rahal JJ Jr. Tissue Penetration of Amphotericin B in Candida Endocarditis. Chest 66:376-77, 1974.

24. Hyams P, Simberkoff MS, Rahal JJ Jr. Synergy Between Cephalosporin and Aminoglycoside Antibiotics Against *Providencia* and *Proteus* Antimicrob Ag Chemother 5:571-77, 1974.

25. Noreiga ER, Rubinstein E, Simberkoff MS, Rahal JJ Jr. Clinical and Laboratory Evaluation of Cefanone, a New Cephalosporin Antibiotic. Amer J Med Sci 267:353-57, 1974.

26. Rubinstein E, Onderdonk AB, Rahal JJ Jr. Peritonsillar Infection and Bacteremia Caused by *Fusobacter gonidiaformans*. J Pediat 85:673-75, 1974.

27. Rubinstein E, Noreiga E, Simberkoff M, Rahal JJ Jr. Endocarditis Following Cardiac Surgery. Frontiers of Internal Medicine 1974. pp 267-269.

28. Noriega ER, Rubinstein E, Simberkoff MS, Rahal JJ Jr. Subacute and Acute Endocarditis Due to *Pseudomonas cepacia* in Heroin Addicts. Amer J Med 59:29-36, 1975.

29. Rahal JJ Jr, Simberkoff MS, Rubinstein E. Intrathecal Gentamicin (Letter). N Eng J Med 291:533-34, 1974.

30. Noriega ER, Leibowitz RE, Richmond AS, Rubenstein E, Schaeffler S, Simberkoff MS, Rahal JJ Jr. Nosocomial Infection Due to Gentamicin-resistant Streptomycin-sensitive *Klebsiella* J Infect Dis 131:S45-S50, 1975.

31. Rubinstein E, Noriega ER, Simberkoff M, Holzman R, Rahal JJ Jr. Fungal Endocarditis: Analysis of 24 Cases and Review of the Literature. Medicine 54:331-44, 1975.

32. Simberkoff MS, Ricupero I, Rahal JJ Jr. Host Resistance to *Serratia marcescens* Infections: Serum Bactericidal Activity and Phagocytosis by Normal Blood Leukocytes. J Lab Clin Med 87:206-17, 1976.

33. Rahal JJ Jr, Millian SJ, Noriega E. Coxsackie and Adenovirus Infection: Association with Acute Febrile and Juvenile Rheumatoid Arthritis. JAMA 235:2496-2501,1976.

34. Richmond AS, Simberkoff MS, Rahal JJ Jr, Schaeffler S. R-Factors in Gentamicin-Resistant Organisms Causing Hospital Infection. Lancet 2:1176-78, 1975.

35. Rahal JJ Jr, Simberkoff MS, Kagan K. Bactericidal Efficacy of Sch 20569 and Amikacin Against Gentamicin-Sensitive and Resistant Oranisms. Antimicrob Agents Chemother 9:595-99, 1976.

36. Simberkoff MS, Moldover NH, Rahal JJ Jr. Specific and Non-Specific Immunity to *Serratia marcescens* infection. J Infect Dis 134:348-53, 1976.

37. Richmond AS, Simberkoff MS, Schaeffler S, Rahal JJ Jr. Resistance of *Staphylococcus aureus* Phage Type 92 to Semisynthetic Penicillins and Cephalothin. J Infect Dis 135:108-12, 1977.

38. Pollock AA, Berger S, Richmond AS, Simberkoff MS, Rahal JJ Jr. Amikacin Therapy for Serious Gram-Negative Infection. JAMA 237:562-64. 1977.

39. Simberkoff M Rahal JJ Jr. Parenteral Aminoglycoside Antibiotics 1977. New York State J Med 77:81-5, 1977.

40. Cherubin C, Neu HC, Rahal JJ Jr, Sabath LD. The Emergence of Chloramphenicol Resistance in *Salmonella*. J Infect Dis 135:807-12, 1977.

41. Rahal JJ Jr. Antibiotic Combinations: The Clinical Relevance of Synergy and Antagonism. Medicine 57:179-95, 1978.

42. Pollock AA, Berger S, Simberkoff MS, Rahal JJ Jr. Hepatitis Associated with High Dose Oxacillin Therapy. Arch Intern Med 138:915-17, 1978.

43. Rahal JJ Jr. Gram-Negative Meningitis in Adults and Other Unusual Bacterial Infections of the Meninges. In, Handbook of Clinical Neurology, Vol. 33, 1978. H L Klawans, Edit. Infections of the Nervous System, Part I. Chapter 8, pp 97-105. North-Holland Publishing Co., Amsterdam, New York, Oxford.

44. Rahal JJ Jr, Simberkoff MS. Antibiotics: How to Use Them in 1977-78. Special Series. Postgraduate Medicine, Volumes 62-63, September 1977 - August 1978.

45. Rahal JJ Jr, Simberkoff MS. Adverse Reactions to Antimicrobial Agents. Disease-a-Month 15:1-67, October 1978.

46. Bernhardt LL, Antopol SC, Simberkoff MS, Rahal JJ Jr. Association of Teichoic Acid Antibody with Metastatic Sequelae of Catheter-Associated *S.aureus* Bacteremia: A Failure of Two Week Antibiotic Treatment. Amer J Med 66:355-57, 1979.

47. Rahal JJ Jr, Simberkoff MS. Bactericidal and Bacteriostatic Antimicrob Agents Chemother. 16:13-18,1979.

48. Rahal JJ Jr. Diagnosis and Management of Meningitis in Adults Due to Gram-Negative Bacilli. In: Current Clinical Topics in Infectious Diseases 1980. JS Remington and MN Swartz, Edit. McGraw-Hill.

49. Simberkoff M, Moldover N, Rahal JJ Jr. Absence of Bactericidal and Opsonic Activities in Normal and Infected Human Cerebrospinal Fluids. A Regional Host Defense Deficiency. J Lab Clin Med 95:362-72, 1980.

50. Simberkoff M S, Schiffman G, Katz LA, Spicehandler JJ, Moldover NH, Rahal JJ Jr. Pneumococcal Capsular Polysaccharide Vaccination in Adult Chronic Hemodialysis Patients. J Lab Clin Med 96:363-70, 1980.

51. Pollock AA, Stein AJ, Simberkoff MS, Rahal JJ Jr. Netilmicin Therapy of Gentamicin-Sensitive and Resistant Gram-Negative Infections. Am J Med Sci 282:2-11,1981.

52. Rahal JJ Jr. Clinical experience with infections due to methicillin heteroresistant *Staph aureus*. In Beta-lactam antibiotics. Mode of action new developments, and future prospects. Salton R J, Schockman G D, Edit. Academic Press, 1981 pp.531-34.

53. Bernhardt LL, Simberkoff M, Rahal JJ Jr. Deficient Cerebrospinal Fluid Opsonization in Experimental *Escherichia coli* Meningitis. Infection and Immunity. 32:411-413, 1981.

54. Rahal JJ Jr, Simberkoff MS. Treatment of Fungal Endocarditis in, Treatment of Infective Endocarditis. A L Bisno, Edit. American Heart Association, Grune and Stratton, 1981.

55. Rahal JJ Jr, Simberkoff MS. Host Defense and Antimicrobial Therapy in Adult Gram-Negative Bacillary Meningitis. Ann Intern Med 96:468-74, 1982.

56. Spicehandler JJ, Pollock AA, Simberkoff MS, Rahal JJ Jr. Intravenous Pharmacokinetics and *in vitro* Bactericidal Activity of Sulfamethoxazole-Trimethoprim. Rev Infect Dis 4:562-65, 1982.

57. Rahal JJ Jr. Moxalactam Therapy of Gram-Negative Bacillary Meningitis. Rev Infect Dis 4 (Suppl.):S606-S609, 1982.

58. Maslow MJ, Levine JF, Pollock AA, Simberkoff MS, Rahal JJ Jr. Efficacy of a Twelve Hourly Ceftriaxone Regimen in the treatment of Serious Bacterial Infections. Antimicrob Agents Chemother 22:103-7, 1982.

59. Pollock AA, Tee PE, Patel IH, Spicehandler JJ, Simberkoff MS, Rahal JJ Jr. Pharmacokinetic Characteristics of Intravenous Ceftriaxone in Normal Adults. Antimicrob Agents Chemother 22:816-23, 1982.

60. Levine JF, Hiesiger EM, Whelan MA, Pollock AA, Simberkoff MS, Rahal JJ Jr. Pneumococcal Meningitis Associated with Retroperitoneal Abscess. A Rare Complication of Lumbar Puncture. JAMA 248:2308-09,1982.

61. Levine JF, Hanna BA, Pollock AA, Simberkoff MS, Rahal JJ Jr. Streptococcal Endocarditis: Relapse After Penicillin Therapy. Am J Med Sci 286:31-36, 1983.

62. Rahal JJ Jr. Rationale for Use of Antimicrobial Combination in Treatment of Gram Negative Infections. Amer J Med 75:68-71, 1983.

63. Rahal JJ Jr, Simberkoff MS, Landesman SH and the Metropolitan Meningitis Study Group. Prospective Evaluation of Moxalactam Therapy for Gram-Negative Bacillary Meningitis. J Infect Dis 149:562-67, 1984.

64. Maslow MJ, Reitano JM, Schnall HA, Shah AT, Simberkoff MS, Rahal JJ Jr. Myocardial Abscess Due to *Klebsiella pneumoniae* Complicating Acute Infarction. Am J Med Sci 287:58-60, 1984.

65. JJ Rahal Jr, Letter to the Editor. *Staphylococcus aureus*. N Eng J Med 311:796, 1984.

66. Simberkoff MS, El-Sadr W, Schiffman G, Rahal JJ Jr. *Streptococcus pneumoniae* with Acquired Immune Deficiency Syndrome, with Report of a Pneumococcal Vaccine Failure. Am Rev Respir Dis 1984; 130:1174-76.

67. Levine JF, Maslow MJ, Leibowitz RE, Pollock AA, Hanna BA, Schaefler S, Simberkoff MS, Rahal JJ Jr. Amikacin-Resistant Gram-Negative Bacilli: Correlation of Occurrence with Amikacin Use. J Infect Dis 151:295-300, 1985.

68. Rahal JJ Jr.. Therapy of Gram-Negative Bacillary Meningitis in Adults. In Bacterial Meningitis. Sande M A, Smith A L, Root R K.Edit. Churchill Livingstone, N.Y. 1985 pp.193-202.

69. Rahal JJ Jr. Treatment of Methicillin Resistant Staphylococcal Infections. Chapter 44, pp.489-514. In Antibiotics Annual. Peterson PK and Verhoef J, Edit. Elsevier Science Publishers, Amsterdam, 1986.

70. Rahal JJ Jr, Chan YK, Johnson G, and Participants of the VA Cooperative Study. Nafcillin Therapy for *S.aureus* Bacteremia: Outcome and its Relationship to Tolerance, Teichoic Acid Antibody, and Bactericidal Serum Levels. Amer J Med 81:43-52, 1986.

71. Maslow MJ, Simberkoff MS, Rahal JJ Jr. Clinical Efficacy of a Synergistic Combination of Cefotaxime and Amikacin against Multiresistant *Pseudomonas* and *Serratia* Infections. J Antimicrob Agents Chemother 16:227-34, 1985.

72. Zuger A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ Jr. Cryptococcal Disease in Patients with the Acquired Immunodeficiency Syndrome. Ann Intern Med 104:234-40,1986.

73. Simberkoff MS, Rahal JJ Jr. Bactericidal Activity of Ciprofloxacin against Amikacin-and Cefotaxime-Resistant Gram Negative Bacilli and Methicillin-Resistant Staphylococci. J Antimicrob Agents Chemother 17:585-91, 1986

74. Rahal JJ Jr, Simberkoff MS. Comparative Bactericidal Activity of Penicillin-Netilmicin and Penicillin-Gentamicin against Enterococci. J Antimicrob Chemother 17:585-91, 1986.

75. Rahal JJ Jr. Commentary on "Restriction Policies for Therapy With Combination Antibiotics". J Infect Dis 153:647-648, 1986.

76. Berman DS, Schaeffler S, Simberkoff MS, Rahal JJ Jr. Tourniquets and Nosocomial Methicillin-Resistant *Staphylococcus aureus* Infections (Letter). N Engl J Med 315:514-15, 1986.

77. El Sadr W, Sidhu G, Diamond G, Zuger A, Berman D, Simberkoff MS, Rahal JJ Jr. High-Dose Corticosteroids as Adjunct Therapy in Severe *Pneumocystis carinii* Pneumonia. AIDS Research. 2:349-55, 1986.

78. Zuger A, Wolf B, El Sadr W. Simberkoff MS, Rahal JJ Jr. Pentamidine-associated acute pancreatitis. JAMA 256:2383-85, 1986.

79. Berman DS, Schaefler S, Simberkoff MS, Rahal JJ Jr. *Staphylococcus aureus* Colonization in Intravenous Drug Abusers, Dialysis Patients, and Diabetics. J Infect Dis 155:829-31, 1987.

80. Rahal JJ Jr. Therapy of Patients with Resistant Bacterial Infections. Bull N Y Acad Med 63:318:29, 1987.

81. Rahal JJ Jr. Choices of New Penicillins and Cephalosporins in the DRG Era. Current Clinical Topics in Infectious Diseases-Volume 9. Remington J S and Swartz M N, Edit. McGraw Hill Book Co, 1988.

82. Zuger A, Schuster M, Simberkoff MS, Rahal JJ Jr, Holzman RS. Maintenance amphotericin B for cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 109:592-3, 1988.

83. Rahal JJ Jr. Approach to Bacterial Infection of the Central Nervous System. In: Textbook of Internal Medicine; William N. Kelley, Edit. JB Lippincott Company, Philadelphia, 1989. Chapter 329, p.1730-37.

84. Rahal JJ Jr. Editorial-Preventing Second-Generation Complications due to *Staphylococcus aureus*. Arch Intern Med 149:592-93, 1989.

85. Agins BD, Berman DS, Spicehandler D, El Sadr W, Simberkoff MS, Rahal J J. Effect of combined therapy with ansamycin, clofazimine, ethambutol and isoniazid for *Mycobacterium avium* infection in patients with AIDS. J Infect Dis 159:784-87, 1989.

86. Taneja-Uppal N, Rappaport S, Berger BJ, Davidson E, Rahal JJ. Human Immunodeficiency Virus (HIV) Infection and Hemolytic Anemia. Ann Intern Med 111:340-1, 1989.

87. Urban C, Rahal JJ, Dattwyler RJ, Gorevic P, Luft BJ. Penicillin-binding proteins in *Borrelia burgdorferi*. J Bacteriol 172:6139-41,1990.

88. deLencastre H, Figueiredo AMS, Urban C, Rahal J, Tomasz A. Multiple Beta Lactam Resistance Mechanisms in Clinical Isolates of Staphylococcus from a Hospital in New York City. Antimicrob Agents Chemother 35:632-39, 1991.

89. Danna PL, Urban C, Bellin E, Rahal JJ. Role of *Candida* in the pathogenesis of antibiotic-associated diarrhea in the elderly. Lancet 337:511-14, 1991.

90. Rahal JJ. Corticosteroids as adjunctive therapy for pneumocystis pneumonia in patients with AIDS. N Eng J Med (Letter) 324:1666, 1991.

91. Rahal JJ. Resistant staphylococcal infection (Letter). Ann Intern Med 114:9111, 1991.

92. Urban C, Rahal JJ, Luft B. Effect of a beta lactamase inhibitor, tazobactam on growth and penicillin binding proteins of *Borrelia burgdorferi*. FEMS Microbiol Lett 82:113-16, 1991.

93. Urban C, Go E, Mariano N, Berger BJ, Avraham I, Rubin D, Rahal JJ. Effect of sulbactam on infections caused by imipenem-resistant *Acinetobacter calcoaceticus* Biotype anitratus. J Infect Dis 167:448-51, 1993.

94. Rahal JJ. Intestinal overgrowth by *Candida*: Clinically important or not? Infect Dis Clin Pract 2:254-59, 1993.

95. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of Klebsiella infection resistant to late generation cephalosporins. Ann Intern Med 119:353-58, 1993.

96. Urban C, Meyer KS, Mariano N, Rahal JJ, Flamm R, Rasmussen BA, Bush K. Identification of TEM-26 B-lactamase responsible for a major outbreak of Ceftazidime-resistant *Klebsiella pneumonia*. Antimicrob Agents Chemother 38:392-95, 1994.

97. Rubin DS, Rahal JJ. Mycobacterium-avium complex. Infect Clin N Am 8:413-26, 1994.

98. Go ES, Urban C, Burns J, Kreiswirth B, Eisner W, Maiano N, N,Mosinka-Snipas K, Rahal JJ. Clinical and molecular epidemiology of *acinetobacter* infections sensitive only to polymyxin B and sulbactam. Lancet 344:1329-32, 1994.

99. Rahal JJ. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. N Eng J Med 331: 1774-5, 1994 Letter.

100. Urban C, Go E, Mariano N, Rahal JJ. Interaction of sulbactam, clavulanic acid and tazobactam with penicillin-binding proteins of imipenem-resistant and-susceptible *Acinetobacter baumannii*. FEMS Microbiology Letters 125: 193-98, 1995.

101. Bradford PA, Urban C, Jaiswal A, Mariano N, Rasmussen BA, Projan SJ, Rahal JJ, Bush K. SHV-7, a novel cefotaxime-hydrolyzing beta-lactamase, identified in *Escherichia coli* isolates from hospitalized nursing home patients. Antimicrob Agents Chemother 39:899-905, 1995.

102. Sahgal VS, Saw D, Spinucci C, Reuben SW, Rahal JJ, Severe Kikuchi's Disease treated with corticosteroids. Infect Dis Clin Practice 4:315-17, 1995.

103. Sahgal VS, Urban C, Mariano N, Weinbaum F, Turner J, Rahal, JJ. Quinupristin/dalfopristin (RP5900) therapy for vancomycin-resistant *Enterococcus faecium* aortic graft infection. Microbial Drug Resist 1:245-47, 1995.

104. DeMets DL, Fleming TR, Whitley RJ, Childress JF, Ellenberg SS, Foulkes M, Mayer KH, O'Fallon J, Pollard RB, Rahal JJ, Sande M, Straus S, Walter L, Whitley-Williams P. The Data and Safety Monitoring Board and Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials. Controlled Clinical Trials 16:408-21, 1995.

105. Urban C, Mariano N, Mosinka-Snipas K, Wadee C, Chahrour T, Rahal JJ. Comparative *In vitro* activity of SCH 27899, a novel everninomicin, and vancomycin. J Antimicrob Chemother 37:361-64, 1996.

106. Segal-Maurer S, Urban C, Rahal JJ. Current perspectives on multidrug-resistant bacteria: Epidemiology and Control. Infec Dis Clin North Am. 10(4):939-57, 1996.

107. Bradford PA, Urban C, Mariano N, Projan S, Rahal JJ, Bush K. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid mediated Amp C B-lactamase, and the loss of an outer membrane protein. Antimicrob Agents Chemother 41:563-69, 1997.

108. Urban C, Rahal JJ. Klebsiella and extended spectrum B-Lactamases. Int J. Antimicrob Agents 8:7-43, 1997.

109. Segal-Maurer S, Kreiswirth BN, Burns JM, Lim M, Lavie,S. Urban C, Rahal JJ. Mycobacterium tuberculosis specimen contamination revisited: the role of laboratory environmental control in a pseudo-outbreak. Infect Control Hosp Epidemiol 19:2;101-5, 1998.

110. Rahal JJ. Intravascular-catheter-related infection (Letter). Lancet 351:1739, 1998.

111. Rahal JJ, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, Mariano N, Marks S, Burns JM, Dominick D, Lim M. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. JAMA 280:1233-37, 1998.

112. Segal-Maurer S, Mariano N, Qavi A, Urban C, Rahal JJ Jr. Successful treatment of ceftazidime-resistant *Klebsiella pneumoniae* ventriculitis with intravenous meropenem and intraventricular polymyxin B: Case report and review. Clin Infect Dis 28:1134-38, 1999.

113. Ahmad M, Urban C, Mariano N, Bradford P, Calgani E, Projan S, Bush K, Rahal JJ. Clinical characteristics and molecular epidemiology associated with imipenem resistant *Klebsiella pneumoniae*. Clin Infect Dis 29:352-55, 1999.

114. Rahal JJ, Urban C. *Acinetobacter*: Seminars in Respiratory and Critical Care Medicine 21:341-48, 2000

115. Urban C, Mariano N, Rahman N, Queenan AM, Bush K, Rahal JJ. Detection of multiresistant, ceftazidime-susceptible *Klebsiella pneumoniae* isolates lacking TEM-26 after class restriction of cephalosporins. Microbial Drug Resistance 2000;6:297-303.

116. Rahal JJ. Extended spectrum beta-lactamases: how big is the problem? Clin Microbial Infect 2000;6(Suppl.2):2-6.

117. Rahal JJ, Urban C. *Acinetobacter*: Epidemiology and Control - US Experience. In: Infection Control in the ICU Environment. Bonten and Weinstein, Eds. In: Perspectives on Critical Care Infectious Diseases. Kluwer Academic Publishers, 2002:pp.67-76.

118. Urban C, Mariano N, Rahal JJ, Tae E, Ponio c, Koprivnjak T, Weiss J. Polymyxin B-resistant *Acinetobacter baumannii* clinical isolate susceptible to recombinant BPI_{21} and cecropin P1. Antimicrob Agents Chemother 2001;45:994-5.

119. Sorin M, Segal-Maurer S, Mariano N, Urban C, Combest A, Rahal JJ. Nosocomial transmission of imipenem-resistant *Pseudomonas aereuginosa* following bronchoscopy associated with improper connection to the STERIS system 1 processor. Infect Control Hosp Epidemiol 2001;22:409-13.

120. Anderson JF, Rahal JJ. Efficacy of interferon alpha-2b and ribavirin against West Nile virus *in vitro*. Emerging Infect Dis 2002;8:107-8.

121. Urban C, Rahman N, Zhao X, Mariano N, Segal-Maurer S, Drlica K, Rahal JJ. Fluoroquinolone-resistant *Streptococcus pneumonial* associated with levofloxacin therapy. J Infect Dis 2001;184:794-8.

122. Rahal JJ. Short-term therapy for intravascular catheter-related *Staphylococcus aureus* bacteremia (Letter). Clin Infect Dis 2001;33:1946-7.

123. Rahal JJ, Urban C, Segal-Maurer S. Nosocomial antibiotic resistance in multiple gram-negative species: experience at one hospital with squeezing the resistance balloon at multiple sites. Clin Infect Dis 2002;34;499-503.

124. Urban C, Segal-Maurer S, Rahal JJ. Antibiotic resistance in a single hospital: inevitable or avoidable? Amer Soc Microbiol News 2003:69;13-17.

125. Urban C, Segal-Maurer S, Rahal JJ. Considerations in control and treatment of nosocomial infectious due to multi drug resistant *Acinetobacter baumannii*. Clin Infect Dis 2003;36:1268-74.

126. Yoon J, Segal-Mauer S, Rahal JJ. An outbreak of domestically acquired typhoid fever in Queens, N.Y. Arch Intern Med 2004;164:565-7.

127. Urban C, Rahal JJ. (2004) Mechanisms of carbapenem resistance in *Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas Areuginosa*. Rev Med Microbiol (In Press).

128. Yoon J, Urban C, Terzian C, Mariano N, Rahal JJ. *In vitro* double and triple synergistic activities of polymyxin B, imipenem, and rifampin against multi-drug resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother Mar.2004,753-7.

129. Nazir J, Urban C, Mariano N, Burns J, Tommasulo B, Rosenberg C, Segal-Maurer S, Rahal JJ. (2004) Quinolone resistant *Haemophilus influenzae* in a long-term care facility: clinical and molecular epidemiology. Clin Infect Dis 2004;38: June 1.

130. Bradford PA, Bratu S, Urban C, Visalli M, Mariano N, Landman D, Rahal JJ, Brooks S, Cebular S, Quale J. (2004) Emergence of carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 B-lactamases in New York City. Clin Infect Dis (In Press).

131. Qavi A, Segal-Maurer S, Mariano N, Urban C, Lim M, Rosenberg C, Maurer J, Rahal JJ. (2004) Increased mortality associated with clonal outbreak of ceftazidime-resistant *Klebsiella-pneumoniae*: A case control study. Infect Control *Hosp Epidemiol (In Press)*.

132. Rahal JJ, Anderson J, Rosenberg C, Reagan T, Thompson LL. Effect of interferon alpha-2b therapy on St. Louis virus meningoencephalitis: Clinical and laboratory results of a pilot study JID (In Press)